CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761183
Priority or Standard	Class 2 resubmission of priority review
Submit Date(s)	February 17, 2022
Received Date(s)	February 17, 2022
PDUFA Goal Date	November 17, 2022
Division/Office	Division of Diabetes, Lipid Disorders and Obesity (DDLO)/Office of New Drugs (OND)
Reviewer Name(s)	Lauren K. Wood Heickman, MD
Review Completion Date	Electronic stamp
Established/Proper Name	PRV-031/teplizumab-mzwv
(Proposed) Trade Name	Tzield
Applicant	Provention Bio, Inc.
Dosage Form(s)	2 mg/ 2mL single-(b) (4) vial
Applicant Proposed Dosing Regimen(s)	Intravenous infusion given daily for a 14 consecutive day course. The specific dosing regimen is pending finalization of the Office of Clinical Pharmacology review.
Applicant Proposed Indication(s)/Population(s)	Teplizumab is an anti-CD3 humanized monoclonal antibody indicated for the delay of type 1 diabetes in at-risk individuals
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	TZIELD is indicated to delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D

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Glossary

ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
AST	aspartate aminotransferase
AUC	area under the curve
BLA	biologics license application
BSA	body surface area
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CGM	continuous glucose monitor
CLIA	Clinical Laboratory Improvement Amendment
CMV	cytomegalovirus
CR	complete response
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DDLO	Division of Diabetes, Lipid Disorders and Obesity
DKA	diabetic ketoacidosis
DLP	data lock point
DRM	Division of Risk Management
DMC	data monitoring committee
EBV	Epstein-Barr virus
GADA	glutamic acid decarboxylase 65 antibody
FDA	Food and Drug Administration

FDAAA	Food and Drug Administration Amendments Act
IAA	insulin antibody
IA-2A	insulinoma-associated-2-antibody
ICA	islet cell antibody
IND	investigational new drug
INR	international normalized ratio
IV	intravenous
LPD	lymphoproliferative disorder
MedDRA	Medical Dictionary for Regulatory Activities
OCP	Office of Clinical Pharmacology
OGTT	oral glucose tolerance test
OPQ	Office of Pharmaceutical Quality
PCR	polymerase chain reaction
PD	phamacodynamic
PDUFA	Prescription Drug User Fee Act
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PopPK	population pharmacokinetic
PREA	Pediatric Research Equity Act
PT	preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment emergent adverse event
T1D	type 1 diabetes
ULN	upper limit of normal
ZnT8A	zinc transporter 8 antibody

1. Executive Summary

Teplizumab-mzwv (called teplizumab in this review; proposed proprietary name Tzield) is a first-in-class humanized anti-CD3 monoclonal antibody proposed delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients aged 8 years and older with Stage 2 type 1 diabetes.

Please see Summary Memo in DARRTS, dated July 2, 2021, for the original clinical review of this BLA (biologics licensing application). This clinical review contains only new information submitted with the resubmission.

The initial BLA was submitted October 31, 2020 and received a Complete Response action on July 2, 2021. The Office of Clinical Pharmacology (OCP) recommended withholding approval because of deficiencies related to the lack of demonstration of bioequivalence between the to-be-marketed drug product (AGC Biologics product) and the drug product used in clinical studies (Eli Lilly product). In addition, the Office of Pharmaceutical Quality (OPQ) recommended withholding approval because of deficiencies related to the (b) (4) manufacturing site and an unacceptable charge variation measured in PRV-031 drug substance manufactured at AGC Biologics and the resulting drug product under recommended storage conditions. Reviewers from all other review disciplines did not find deficiencies precluding approval.

This Complete Response submission includes new and updated safety information on all reports of death, treatment-emergent adverse events (AEs), serious adverse events (SAEs), AEs leading to study drug discontinuation reported with the Data Lock Point (DLP) date of November 24, 2021, from 550 subjects with recent-onset stage 3 T1D from two ongoing trials (PROTECT and TN-10 extension) and the completed Protégé extension trial. The largest study included in the safety update, the PROTECT study, is an ongoing randomized placebo control trial in which 327 subjects were randomized to teplizumab or placebo in a 2:1 ratio and is currently blinded. The blinded data from the PROTECT study were useful for interpreting laboratory related adverse events and adverse events of low baseline frequency in the population being studied: specifically serious infections, cytokine release syndrome, and hypersensitivity analyses. The TN-10 extension study is an open-label extension study to the TN-10 trial reviewed in the original BLA and contained safety data for 4 subjects who were dosed with teplizumab open-label. Protégé Extension was a noninterventional follow-up study to the Protégé study, a study that was included in the original BLA submission. The safety update

included long-term safety data for 181 participants given teplizumab during the original Protégé study, and safety update analyses were limited to long-term adverse events.

Cytokine release syndrome, infection, laboratory-related adverse events (mainly lymphopenia and liver enzyme elevations), and rash, are all adverse events noted in the original teplizumab safety studies and were observed in similar rates and severity in patients in the safety population as previously reported in the original BLA submission. Less stringent laboratory-based discontinuation criteria were used for the PROTECT study, with notably decreased frequency of premature treatment discontinuations, with approximately half the rate observed in the original BLA submission. On review of the individual narratives for each laboratory adverse-event related discontinuation event there were no serious adverse events related to continued treatment among patients who would have met the prior safety database premature treatment discontinuation criteria. This reviewer therefore concludes that more serious or permanent harms are not expected if less restrictive discontinuation criteria (from the PROTECT study) are reflected in teplizumab's labeling. Additionally, the PROTECT study provided reassuring support that laboratory related adverse events were reversible.

In addition to adverse event reporting, the safety update provided information on ADA formation in the to-be-marketed drug product (AGC Biologics) in comparison to the clinical trial (Lilly) drug product through the unblinded analysis of a pharmacokinetic (PK) / pharmacodynamic (PD) substudy of the PROTECT safety update study as well as information on adverse events experienced in patients given the AGC vs. Lilly products through blinded adverse event analyses of the PROTECT study. This analysis demonstrated that the AGC product was associated with earlier appearance of anti-drug antibodies (ADA) and higher ADA titers than the Lilly product.

After review of this safety update, teplizumab continues to have an acceptable safety profile for its intended use in adults and children aged 8 years or older with stage 2 type 1 diabetes. Additionally, the AGC drug product, which is intended to be used as the drug product in the post market setting was demonstrated to have a similar safety profile to the Lilly AGC product.

1.1. Conclusions on the Substantial Evidence of Effectiveness

See Summary Basis for Approval memo in DARRTS, dated July 2, 2021.

1.2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment
See Summary Basis for Approval in DARRTS, dated July 2, 2021. The B-R-A is unchanged from the original conclusions.

2. Regulatory Background

2.1. Summary of Presubmission/Submission Regulatory Activity

The original teplizumab BLA 761183 was submitted on October 31, 2020 and received a Complete Response on November 2, 2020. For a detailed account of regulatory activity prior to resubmission, please see the primary clinical review dated July 2, 2021. The Complete Response (CR) Letter was issued to the Applicant on July 2, 2021, stating that the FDA could not approve the application in its present state due to the lack of biocomparability between the PRV-031 product used in the clinical safety studies submitted in the original BLA, manufactured by Eli Lilly, and the planned commercial product, manufactured by AGC Biologics. In particular, the PK bridging study, PRV-031-004, failed to show PK comparability between the teplizumab product used in the TN-10 study and the planned commercial product. Additionally, a lack of an acceptable facility inspection at the (b) (4) manufacturing facility, an unacceptable charge variation measured in teplizumab drug substance manufactured at AGC Biologics and the resulting drug product under recommended storage conditions were cited as additional reasons for CR. Other comments were provided by clinical, clinical pharmacology and product quality teams that were not considered approvability issues, including the recommendation to characterize the immunogenicity potential of the proposed commercial product (AGC Biologics) to the clinical trial product (Lilly) and provide justification for any differences noted.

During the weeks after the CR, the sponsor and the Agency exchanged communications regarding the initial Content and Format Package proposal for the safety update. The Agency provided acceptance of the plan for the proposed content of the safety update on July 15, 2021, by general advice letter with the additional recommendation to include an updated analysis of adverse events of special interest (AESI).

On July 27, 2021, the Sponsor submitted an amendment to IND 100262 containing the statistical analysis plan (SAP) for a planned PK/PD substudy for the ongoing PRV-031-001 (PROTECT) study in order to address the concerns related to bioequivalence noted in the complete response letter, as both the clinical trial (Eli Lilly) product and the to-be-marketed (AGC Biologics) product were used as investigational products in the PROTECT study allowing for PK, PD, and immunogenicity comparisons between the products. The Agency replied with an Advice/IR letter on August 6, 2021, in which we strongly recommended the population pharmacokinetic (popPK) model and analysis plan be pre-specified and discussed with the Agency before unblinding of the PROTECT PK/PD and immunogenicity data and that all data

from the PRV-031-004 (single-dose healthy patient bioequivalence study), Protégé study, TN-10 study, and PROTECT study be built in a single (joint) popPK model.

On August 17, 2021, the Sponsor submitted a proposed BLA PK/PD data package and anticipated timelines to support comparability in response to our August 6, 2021, Advice/IR letter. The Sponsor sent a follow up email on August 25, 2021, seeking agreement with the proposed statistical analysis plan (SAP) in order to proceed with data transfer of unblinded PK data to the (b) (4) teams. A subsequent Advice/IR letter was issued on September 1, 2021, stating review expectations and providing comments and recommendations on the SAP and modeling and simulation analysis plan. The Sponsor then requested an informal teleconference for clarification purposes, which was held on September 3, 2021. On September 9, 2021, the Agency confirmed agreement with the Sponsor's proposed approach for the amended two stage PK/PD model design via email.

Concurrent with the clinical pharmacology Sponsor meetings and discussions, a Type A CMC Meeting was held on August 31, 2021, via teleconference with discussion on the planned content to address CMC issues contained in the complete response letter. Meeting minutes are available in DARRTs, checked in on September 22, 2021.

A Type A meeting was held on November 18, 2021 (refer to meeting minutes in DARRTS dated December 8, 2021). The Agency provided feedback on the Sponsor's proposed single joint population PK (popPK) model from the Protégé study, TN-10 study, study PRV-031-004 and the PROTECT study. The goal of this model was to characterize the differences in PK between the teplizumab (PRV-031) products from Lilly and AGC Biologics. The Agency provided recommendations in order to ensure the popPK model captures the difference in PK between products in a consistent manner and avoid study specific effects as much as possible.

A Type B meeting was held for IND 100262 (at-risk population, the IND associated with pre-BLA 761183) on January 25, 2022. The purpose of this meeting was to discuss and obtain agreement on the Sponsor's proposed clinical pharmacology data package as well as the clinical contents for the BLA 761183 resubmission. The preliminary safety update was submitted to the Agency at this meeting, and the Agency agreed that the submitted update was adequate for review with the addition of analyses that use the same definition of hypoglycemia as used in the original BLA submission to assess the safety population in the update, in addition to analyses using revised definitions as well as the inclusion of updated exposure information for the clinical trials in person-time. Additionally, at this meeting the Agency recommended that the Sponsor propose an alternative full 14-day dosing regimen to match the AUC_{inf} and/or C_{trough} exposures between the Lilly and AGC products, using PK simulations from the PROTECT study and individual PK parameters of the Agency-recommended model. It was also recommended

that they provide safety justifications for the modified full 14-day dosing based on previously studied higher dose regimens, as applicable.

On February 17, 2022, the Sponsor submitted the BLA resubmission under review, which included a 13-month safety update, a proposal for 4 alternative dosing regimens (Regimens A-D) with safety justification for the proposed regimens as well as requested pharmacokinetic (PK) comparability data from the PROTECT PK/PD substudy along with requested analyses of concentration-CD3 occupancy analyses, anti-drug antibody (ADA) comparisons between clinical trial and manufactured products.

On June 10, 2022, the Agency sent a Mid-cycle Communication and IR in order to propose an alternative 14-day dosing regimen for the manufactured (AGC) product which met bioequivalence criteria for the pharmacokinetic (PK) model-predicted AUC_{inf}, C_{trough} and C_{max} exposures of clinical trial (Lilly) product derived from both individual (conditional) PK simulations as well as typical (population or average) PK simulations. In this Mid-cycle communication, the Agency confirmed that the Sponsor's proposed regimens did not pass bioequivalence criteria, requesting that the Sponsor also re-run their analyses to confirm this approach. The subsequent submission by the Sponsor including the revised analyses constituted a major amendment, communicated to the Sponsor on June 29, 2022, with a change in Prescription Drug User Fee Act (PDUFA) date from August 18, 2022, to November 17, 2022.

2.2. Devices and Companion Diagnostic Issues

During the initial BLA review cycle, the potential requirement for the development of pancreatic islet autoantibody assays as a companion diagnostic was discussed with the Center for Devices and Radiological Health (CDRH) since T1D autoantibody testing is required for the identification of stage 2 type 1 diabetes. The sponsor has not codeveloped companion diagnostics for the islet autoantibody assays used to identify the intended patient population. In the TN-10 study, patients were selected using islet autoantibody assays developed by the (b) (4) The assays used in the TN-10 study were Clinical Laboratory Improvement Amendment (CLIA)-certified but not FDA-authorized and the Applicant has not specified FDA-authorized assays in their proposed the product labeling. A discussion of the autoantibody assays used in the TN-10 study and their performance characteristics is included in Section 6.1.1.3 of the original BLA review.

Following the BLA resubmission, the need for a companion diagnostic(s) was revisited. Dr. Jessica Chu completed the CDRH consult review, dated June 10, 2022. Her assessment is summarized below:

- Autoantibody testing is necessary to identify patients. Because autoantibody testing is necessary but not sufficient to determine patient eligibility for teplizumab, it is a key determinant in the staging of T1D. Thus, these tests would meet the definition of companion diagnostic devices. They would be essential for the safe and effective use of teplizumab because they would identify patients in whom teplizumab has been studied for safety and effectiveness (i.e., patients with two or more autoantibodies and dysglycemia, but not meeting criteria for the diagnosis of T1D). These are the patients most likely to benefit from teplizumab treatment, and there is insufficient information about the safety and effectiveness of teplizumab in any other population.
- Autoantibody testing is not standard of care. It is not clear that practicing clinicians would correctly identify the population in whom teplizumab has been studied for safety and effectiveness because autoantibody testing for T1D staging is not considered standard of care and these tests are not routinely recommended in clinical practice.
- The autoantibody assays are not standardized, and their performance has not been validated by FDA in the intended population of Stage 2 T1D. There is a lack of assay standardization and their performance in the teplizumab intended use population is uncertain. The laboratory developed tests (i.e., CLIA-certified) have not been reviewed by FDA and the performance of the FDA-authorized tests have been established in a different patient population: to "aid in the diagnosis of Type 1 diabetes mellitus", which is different from a test used to screen for individuals with Stage 2 T1D eligible for teplizumab treatment.
    - Clinical sensitivity for the FDA-authorized tests was determined by assessing true positive test results for samples from diagnosed T1D patients and clinical specificity was determined by assessing true negative test results for samples from patients with non-target diseases (e.g., type 2 diabetes, metabolic syndrome, autoimmune diseases, infection, renal disease, testicular cancer, kidney disease).
    - It is not clear that the sensitivity of the FDA-authorized tests would be the same for diagnosed T1D patients vs. stage 2 T1D patients and that the specificity of the authorized tests would be the same in the non-target disease groups vs. patients suspected of Stage 2 T1DM but determined to be ineligible for the drug.

Dr. Chu concluded by stating, "Without information to understand the performance of the cleared tests in the teplizumab intended use population, we are unable to conclude that cleared tests have high specificity (low false positive rate) in the teplizumab intended use population."

DDLO extensively discussed and considered the advice of CDRH. We agree that autoantibody testing is required to identify the indicated population for teplizumab. However, we disagree with their conclusion that autoantibody testing is not standard of care and that the performance of the FDA-cleared autoantibody assays is unknown.

The limited available precedent for the development of a companion diagnostic outside of the oncology space, wherein companion diagnostics are typically used to select a subgroup of patients where the safety and efficacy of a drug has been adequately demonstrated, was discussed. An example of such testing includes the first companion diagnostic, a test which identified a subgroup of patients with breast cancer which overexpress the HER-2 protein in order to qualify for treatment with Herceptin (trastuzumab). Companion diagnostics have not typically been codeveloped for autoimmune biomarkers utilized to diagnose a variety of autoimmune diseases (e.g., Hashimoto's thyroiditis and celiac disease), where testing is readily available and commonly used in clinical practice. In addition, it was discussed how the use of autoantibody assays are routinely used in clinical practice to identify type 1 diabetes, i.e., a disease state and not a subgroup of patients with a disease state. It was noted that HbA1c, is commonly used in the diagnosis of type 2 diabetes, but not considered a companion diagnostic for drugs intended for the treatment of type 2 diabetes.

The identification of stage 2 T1D relies on the measurement of islet autoantibodies and glycemia. In the case of islet autoantibodies, there are two standard screening approaches. One consists of global assessment of Islet Cell Cytoplasmic Autoantibodies, also known as Islet Cell Antibodies (ICA), typically used as a non-specific screening test to prompt more specific testing as to which antigens are targeted in case of a positive ICA. The second approach, more commonly used today, is to directly test for the four specific antigens targeted by the islet cell antibodies. Currently, if there is suspicion that an individual is at risk of developing T1D, they are tested for the four islet cell autoantibodies directed at specific islet antigens: insulin antibody (IAA), glutamic acid decarboxylase 65 antibody (GADA), Insulinoma-Associated-2-antibody (IA-2A), islet cell antibody (ICA), and zinc transporter 8 antibody (ZnT8A). If positive for two, they are diagnosed with T1D. However, definitive staging depends not on the results of the autoantibody tests, but on whether they have dysglycemia on oral glucose tolerance testing (Stage 2) or overt hyperglycemia and/or symptoms (Stage 3). There are FDA-authorized versions of the 4 specific T1D autoantibody tests available (IAA, GADA, IA-2A and ZnT8A), indicated "as an aid in the diagnosis of Type 1 diabetes mellitus (autoimmune mediated diabetes)".

The following regulatory, scientific, and clinical issues were considered when making the determination as to whether a companion diagnostic would be required:

1. Is the assessment of pancreatic islet cell autoantibodies considered standard of care to aid in the diagnosis of type 1 diabetes?

This reviewer considers T1D autoantibody testing to be standard of care to aid in the diagnosis of patients with type 1 diabetes. Pancreatic islet autoantibodies are commonly used in the identification of patients with type 1 diabetes in two main settings: in clinical research investigating therapeutics intended to delay progression in individuals who meet clinical criteria for early diagnosis of T1D (stage 2 T1D with dysglycemia), and at the time of stage 3 T1D diagnosis (with overt hyperglycemia) to aid in the differentiation of type 1 autoimmune diabetes from type 2 diabetes when the clinical diagnosis is unclear. Stage 2 T1D is also a diagnosis recognized by professional societies responsible for the care for T1D patients (Juvenile Diabetes Research Foundation, Endocrine Society, and American Diabetes Association)[1] and diagnostic requirements have been clearly delineated in the American Diabetes Association Position Statement for the Classification and Diagnosis of Diabetes annual reports since 2017. The criteria for Stage 2 T1D diagnosis are also currently available in the 2022 diagnostic guidelines,[1] with two or more "islet autoantibodies" specified in the diagnostic criteria as well as dysglycemia on oral glucose tolerance testing.

2. Do the clearances for the FDA-authorized islet autoantibody tests, which were validated in patients with new-onset T1D, apply to the population of teplizumab's intended use: stage 2 T1D?

This reviewer considers stage 2 and stage 3 T1D to be stages of the same disease pathophysiology, although representing different time points along the same disease continuum. Stage 3 T1D only differs from stage 2 T1D by the severity and degree of progression, namely the severity of dysglycemia, which determines the presence of clinical symptoms. The 6-month, 2-year, and 4-year risk of progression to stage 3 T1D once patients have dysglycemia and stage 2 T1D, is approximately 25%, 60%, and 75%, and the lifetime risk approaches 100%.[2] Therefore, this reviewer considers pancreatic islet autoantibody testing to be used as part of standard of care to aid in the diagnosis of type 1 diabetes, a disease state which includes both stage 2 and stage 3 T1D.

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[1] American Diabetes Association Professional Practice Committee; 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. Diabetes Care 1 January 2022; 45 (Supplement_1): S17–S38. https://doi.org/10.2337/dc22-S002

[2] Krischer, JP, 2013, The use of intermediate endpoints in the design of type 1 diabetes prevention trials, Diabetologia, 56(9):1919-1924

3. For the FDA-authorized versions of the islet autoantibodies, is there sufficient evidence to support the appropriate detection of teplizumab's intended use population?

As mentioned above, there are FDA-authorized versions of the islet autoantibody tests needed to identify stage 2 T1D (GADA, IAA, IA-2A, and ZnT8A) intended "as an aid in the diagnosis of Type 1 diabetes mellitus (autoimmune mediated diabetes)". Cleared and validated tests which "aid in the diagnosis" of a disease rely on validation studies where the assay has been tested in a population who also have signs and symptoms of the disease. As stage 2 T1D diagnostic criteria include dysglycemia, an important sign of diabetes indicating beta cell dysfunction and dysregulation of insulin secretion, DDLO considers islet autoantibody testing to appropriately be considered a test which aids in the diagnosis of type 1 diabetes mellitus.

A fifth islet autoantibody biomarker, Islet cell antibodies (ICA) were also used in the TN-10 trial to identify patients with Stage 2 T1D. For this test, ICA, there are no currently available FDA-authorized assays available for provider use. This test was requisite in the identification of 9 subjects in TN-10 (5 teplizumab-treated and 4 placebo-treated). When islet cell cytoplasmic autoantibody results were disregarded, 39/44 (89%) teplizumab-treated and 28/32 (88%) placebo treated patients would have met criteria for TN-10 enrollment by use of FDA-authorized T1D autoantibody tests alone. As there is no FDA-authorized version of ICA available, in the postmarketing period, if ICA is intended to be used as a screening methodology to identify patients who qualify for teplizumab use, we recommend ICA be developed as a FDA-authorized companion diagnostic in order to ensure it adequately meets FDA requirements.

4. Is a companion diagnostic required for safe and effective use of teplizumab?

As FDA-authorized versions are available for 4 of the 5 T1D autoantibody tests, we have determined that the currently available islet autoantibody tests are appropriate for the safe and effective use of teplizumab and therefore, we find it unnecessary to require the Applicant to develop these tests as companion diagnostics. Additionally, if we were to recommend companion diagnostics be developed for each one of these tests, we would greatly limit access to patients, as the FDA-authorized tests are commonly available. Moreover, DDLO strongly concludes that the currently available testing and methodology for the identification of stage 2 T1D is appropriately rigorous that the risk of inappropriate diagnoses and use of teplizumab would be very low. This is related to the need for not only multiple positive autoantibodies which is exceedingly rare in the general population, but the additional need for dysglycemia on the oral glucose tolerance test. For example, each individual islet autoantibody assay is calibrated to be highly specific for type 1 diabetes, with specificities of 98.0-98.6% for each of the FDA-authorized tests and when used as a panel, the specificity has been demonstrated to

be as high as 100%.[3] In addition to this reassuring level of specificity, there is evidence from longitudinal studies in patients followed for the development of T1D, that autoantibody titers slightly decrease, or persist at the same level over time.[4] Therefore, the titers of islet autoantibodies (used to generate the diagnostic cutoff) are generally lower once patients are diagnosed with stage 3 T1D. Although FDA-authorized islet autoantibodies were validated in patients with stage 3 T1D, applying this testing to stage 2 T1D would, in theory, result in slightly less sensitive test, but with greater specificity for T1D in the stage 2 population. Moreover, a patient without dysglycemia would not be eligible to get treatment with teplizumab regardless of the laboratory used for islet autoantibody screening. In patients with dysglycemia, the risk of false positives is extremely low given that disease has progressed to the point of beta cell dysfunction, a crucial component of the diagnosis of stage 2 T1D. The presence of dysglycemia both improves the specificity and reliability of the clinical diagnosis of stage 2 T1D.

Conclusion on whether a companion diagnostic will be required:

Based on the regulatory, scientific, and clinical considerations listed above, this reviewer believes that the currently available FDA-authorized tests are appropriate for the diagnosis of stage 2 T1D and identification of patients who may qualify for teplizumab. Recommending a companion diagnostic be developed in this case would create undue burden on patients who qualify for teplizumab use by limiting access to tests which have been demonstrated to appropriately identify patients for teplizumab's intended use.

For ICA, the only islet autoantibody without an FDA-authorized version, we recommend this test require development as a companion diagnostic in the post-marketing period. Additionally, the sponsor will need to bridge the performance of the ICA autoantibody assays used in clinical trials to the companion diagnostic device in the post-marketing period.

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[3] Verge CF, Stenger D, Bonifacio E, Colman PG, Pilcher C, Bingley PJ, Eisenbarth GS. Combined use of autoantibodies (IA-2 autoantibody, GAD autoantibody, insulin autoantibody, cytoplasmic islet cell antibodies) in type 1 diabetes: Combinatorial Islet Autoantibody Workshop. Diabetes. 1998 Dec;47(12):1857-66. doi: 10.2337/diabetes.47.12.1857. PMID: 9836516.

[4] Köhler M, Beyerlein A, Vehik K, Greven S, Umlauf N, Lernmark Å, Hagopian WA, Rewers M, She JX, Toppari J, Akolkar B, Krischer JP, Bonifacio E, Ziegler AG; TEDDY study group. Joint modeling of longitudinal autoantibody patterns and progression to type 1 diabetes: results from the TEDDY study. Acta Diabetol. 2017 Nov;54(11):1009-1017. doi: 10.1007/s00592-017-1033-7. Epub 2017 Aug 30. PMID: 28856522; PMCID: PMC5645259.

3. Sources of Clinical Data and Review Strategy

For this resubmission, I reviewed the sponsor's submitted analyses for the safety update studies: the ongoing PROTECT and TN-10 extension studies and the completed Protégé Extension study. A summary of each study and its role in the safety update review is outlined in Table 1. I also reviewed individual patient narratives for all SAE, discontinuation events, and adverse events of special interest (AESI) in order to determine whether the additional safety data submitted in this resubmission altered the overall safety profile for teplizumab beyond the original review.

Table 1. Trials Included in the Safety Update & Role in Review

Trial	Study Description & Population	Role in the Review
PRV-031-001 (PROTECT)	Ongoing, randomized, double-blind, placebo-controlled, multicenter and multinational trial evaluating the safety and efficacy of teplizumab Patients aged 8-17 years newly diagnosed with T1D (within 6 weeks of diagnosis) treated with teplizumab (Lilly or AGC Biologics) or placebo	As this study is still blinded, I evaluated SAE, TEAE and AESI for: - unexpected safety signals - expected events with teplizumab use that are considered to be rare in the general population (i.e., cytokine release syndrome, lymphopenia, infection) Analysis of immunogenicity between Lilly and AGC Biologics products
PRV-031-002 (TN-10 Extension)	Open-Label Extension of TN-10 study Teplizumab and placebo-treated subjects who participated in the TN-10 trial (at-risk with stage 2 pre-symptomatic T1D) who were diagnosed with stage 3 T1D participated in this open-label study	Limited evaluation for SAE, TEAE, and AESI based on small sample size (N=4)
CP-MGA031-02 (Protégé Extension)	Non-interventional extension, long-term follow-up study for the open-label (segment 1) and double-blind, placebo controlled (segment 2) Protégé study (CP-MGA031-01). Teplizumab and placebo-treated subjects were invited to participate if they completed the Protégé study through Day 728	Evaluation of long-latency events (ex: malignancy) as this was a non-interventional long-term follow up study

My approach to each study in the safety update differed depending on the type of study, and thus studies were reviewed individually in section 5. For instance, blinded results of the ongoing clinical study (PROTECT) were primarily evaluated for unexpected safety signals or for events that are considered to be rare in the general population (laboratory related adverse events, cytopenias, severe infections and cytokine release syndrome) as well as a review of the comparative immunogenicity between Lilly and AGC Biologics products.

There was minimal data from the open-label TN-10 extension study (4 subjects) included in this safety update, and therefore review of TN-10 extension was limited in scope and conclusions. My review for the completed clinical study (Protégé Extension) was limited to assessment of safety signals associated with long-latency events like malignancy, as this study was limited to long-term safety data.

I did not address efficacy other than summarizing findings from the original BLA review (submitted July 2, 2021) and a discussion in Section 4.1.1 when I review how efficacy conclusions have been incorporated into the labeling strategy for this resubmission review.

4. Integrated Review of Effectiveness

4.1. Additional Efficacy Considerations

4.1.1. Considerations on Benefit in the Postmarket Setting

Discussions of benefit in the postmarket setting were deferred in the original clinical review because of the planned Complete Response action. It was noted that the to-be-marketed product should be demonstrated comparable (PK or other method) to the clinical trial product in order to conclude that efficacy in the postmarket setting will be similar to the treatment effect observed in the clinical development program.

In the postmarket setting, teplizumab is anticipated to have a similar treatment effect as was observed within the context of the clinical development program. This determination is based on several important considerations of how teplizumab's use may differ in the postmarket setting and could potentially affect treatment efficacy:

- Potential differences in islet autoantibodies used in screening to detect Stage 2 T1D in patients selected for teplizumab use
- Potential differences in efficacy in subpopulations not represented in the clinical trials: specifically, non-relatives of patients with T1D and patients not included in clinical trials

due to inclusion or exclusion criteria

Restriction of screening for Stage 2 T1D to include the 4 FDA-authorized islet autoantibodies (without ICA)

As detailed in section 2.2 Devices and Companion Diagnostic Issues, there are currently FDA-authorized versions of four of the available five pancreatic islet autoantibodies which were used for the screening and detection of patients with Stage 2 T1D for the TN-10 study. Our division proposes that the only autoantibody without an FDA-authorized version, islet cell antibody (ICA), be developed as a companion diagnostic device. While labeling has not yet been determined, it is possible that teplizumab's label will specify use of an FDA-authorized version of the 4 islet autoantibody tests available, insulin antibody (IAA), glutamic acid decarboxylase 65 antibody (GADA), Insulinoma-Associated-2- antibody (IA-2A), and zinc transporter 8 antibody (ZnT8A) when making a diagnosis of Stage 2 T1D. In the TN-10 study, the number of subjects from each study arm who would have met criteria for enrollment based on results from a four-islet autoantibody panel (IAA, GADA, IA-2A, ZnT8A) alone – disregarding islet cell antibody (ICA) laboratory results are 39 of 44 (89%) teplizumab and 28 of 32 (88%) placebo patients. While this labeling recommendation may limit the number of patients who qualify for teplizumab use in the postmarket setting by 11-12%, it is not expected to lead to a difference in efficacy, as post hoc analyses did not demonstrate a difference in efficacy after exclusion of the 9 subjects who met criteria by ICA positivity.

Expansion of the treatment indication to include non-relatives

Recruitment and enrollment of patients with stage 2 T1D for the TN-10 study was through the TrialNet Pathway to Prevention (TN-01). This screening mechanism facilitated the enrollment of relatives of patients with T1D through active surveillance of families with T1D. Family history is not part of the Stage 2 T1D definition according to professional guidelines[3,4] and the efficacy outcome of the development program is considered applicable to both Stage 2 T1D patients with or without family history. The pathogenesis and risk of progression for stage 2 T1D individuals who are not T1D relatives are not considered to be significantly different from the population studied in TN-10[5], and therefore expansion of the treatment indication to include non-relatives is recommended and was generally supported the Advisory Committee meeting. This change is not expected to have an effect on the benefits of teplizumab treatment in the postmarket setting.

Expansion of Inclusion/Exclusion Criteria

[5] Ziegler, AG, M Rewers, O Simell, T Simell, J Lempainen, A Steck, C Winkler, J Ilonen, R Veijola, M Knip, E Bonifacio, and GS Eisenbarth, 2013, Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children, Jama, 309(23):2473-2479.

As discussed in section 6.1.1.3 of the original BLA review, the Applicant implemented several inclusion and exclusion criteria that are likely unnecessary in the post-market setting such as excluding subjects with a history of asthma or atopic disease. However, the implementation of these criteria is not expected to have an impact on teplizumab's efficacy in the post-marketing setting. Exclusion criteria that have clinically meaningful implications, including excluding those with active infections, or patients with cytopenias or aminotransferase elevations at baseline will be recommended for labeling. For TN-10, the Applicant limited enrollment to subjects weighing ≥26 kg, which is approximately 50th percentile for pediatrics 8 years of age. Therefore, teplizumab may be administered to pediatric patients <26 kg in real-world use. This is not expected to impact the efficacy of teplizumab, as dosing is based on body surface area (BSA).

Defining islet autoantibody positivity and dysglycemia in the postmarket setting
Another consideration for applicability of efficacy benefit in the post-market setting relates to the definition of islet autoantibody positivity and dysglycemia applied in the TN-10 study. TN-10 required confirmatory positivity of two or more pancreatic islet autoantibodies on two separate tests, as well as two dysglycemic oral glucose tolerance tests (OGTT), i.e., a secondary "confirmatory" dysglycemic OGTT in patients who are >18 years prior to enrollment in TN-10. This methodology was considered useful to ensure appropriate subject selection for the interpretation of efficacy in the original BLA efficacy review. Recommending a second screening for islet autoantibodies in the postmarket setting would be a burdensome requirement to enact, given that there is evidence that once two or more islet autoantibodies are detected, the development of dysglycemia on OGTT confirms that the degree of islet cell destruction has reached a threshold that is associated with disease progression.[3] The inclusion of a secondary test for dysglycemia is considered to be much less burdensome to patients and there is evidence from the literature that a second confirmatory OGTT improves the specificity of the Stage 2 T1D diagnosis in older patients (age >18 years). In general, the persistence of dysglycemia on OGTT has been observed to be variable, among patients with 2 or more pancreatic islet autoantibodies. However, among patients younger than age 13 years with a single dysglycemic OGTT, the risk of subsequent development of Stage 3 T1D is extremely high, with an estimated 5-year risk of progression of 94% once a single dysglycemic OGTT is obtained (even if subsequent OGTTs are normoglycemic).[6] It is important to note that for ages 13-18 years in TN-10 the efficacy of teplizumab was not significantly different than in other age subsets and a second confirmatory OGTT was not required in this age group. Therefore, we recommend a second confirmatory dysglycmic OGTT for patients >18 years of age in order to ensure the efficacy of teplizumab in the postmarket setting is consistent with the efficacy

[6] Sosenko JM, Palmer JP, Rafkin-Mervis L, et al. Incident dysglycemia and progression to type 1 diabetes among participants in the Diabetes Prevention Trial-Type 1. Diabetes Care. 2009;32(9):1603-1607. doi:10.2337/dc08-2140

observed in the TN-10 trial.

5. Review of Safety

The safety update includes new and updated safety information for two ongoing trials (PROTECT and TN-10 extension) and the completed observational Protégé Extension trial (Table 2).

The data lock point (DLP) date used for the safety update in the Resubmission is November 24, 2021. See Table 2 below for details.

Table 2. Trials Included in the Safety Update

Trial	Study Design & Population	Subjects	Treatment & Follow-up	Data Included
PRV-031-001 (PROTECT) (US, Canada, Belgium, Czech Republic, France, Germany, UK, Poland)	Ongoing, Randomized, Placebo-controlled, Double-blind multinational, multicenter trial Children (age 8-17 years) with newly diagnosed T1D, within 6 weeks of diagnosis	N=327 Currently Blinded, Randomized 2:1 Teplizumab: Placebo	Teplizumab or placebo in two 12-day IV courses, second course at week 26 or 52 Day 1: 106 μg/m^2 Day 2: 425 μg/m^2 Days 3-12: 850 μg/m^2 Total per course: 9.0 mg/m^2 Follow up: 18 months	From trial start to current data cut-off (11/24/2021) as this trial is ongoing
PRV-031-002 (TN-10 Extension) (5 sites in the US)	Open-Label Extension of TN-10 study Teplizumab and placebo-treated subjects (age 8 and older) who participated in the TN-10 trial (at-risk with stage 2 pre-symptomatic T1D) who have been diagnosed with stage 3 T1D	N=4 Open-label Teplizumab	Teplizumab administered open-label in single 12-day IV course: Day 1: 106 μg/m^2 Day 2: 425 μg/m^2 Days 3-12: 850 μg/m^2 Total per course: 9.0 mg/m^2 Follow up: 18 months	From trial start to current data cut-off (11/24/2021) as this trial is ongoing
CP-MGA031-02 (Protégé Extension) (US, Czech Republic, Estonia, India, Israel, Latvia, Poland,	Non-interventional extension/follow-up study for the Protégé study (CP-MGA031-01). Teplizumab and placebo-treated subjects who	N=181 Teplizumab N=32 Placebo	No intervention was administered Follow up: median 6 months for teplizumab-treated subjects and median 4.5 months for placebo subjects	All data: from extension trial start to trial end (June 2011) This study was terminated prematurely

Romania, Spain, Sweden, Ukraine)	completed the Protégé study through Day 728			

Source: Clinical Reviewer
UK=United Kingdom; US=United States

In the safety update submission, the Sponsor included all reports and narratives for deaths, serious adverse events (SAEs), adverse events leading to study drug discontinuation, and Adverse Events of Special Interest (AESI) for each trial.

Composite frequencies of Treatment-Emergent Adverse Events (TEAEs) were summarized by treatment arm and reported separately for each of the 3 studies in the safety update. As with the original BLA safety analyses submitted by the sponsor, treatment-emergence was defined as occurring any time after the first treatment day, and therefore any adverse event reported during the follow up period was defined as a TEAE. In the primary review for the original BLA, TEAEs were limited to either the 14-day treatment period, or to within 2 weeks of the last dose of study drug. Therefore, TEAE analyses provided by the sponsor could not be directly compared to the TEAE analyses conducted in the original BLA review. Instead, where indicated, TEAE frequencies were compared to the sponsor's original TEAE analyses, which used the same definition of TEAE.

Exposure in Trials Included in the Safety Update

Total exposure and the number of teplizumab courses administered in each study are summarized in Table 3 for the safety update population.

Table 3. Summary of Exposure and Teplizumab Courses Administrated (Safety Update Population)

		PROTECT N=327 (Teplizumab or placebo with 2:1 randomization)	TN-10 Extension Open-Label Teplizumab N=4	PROTÉGÉ Extension Teplizumab Group N=181	PROTÉGÉ Extension Placebo Group N=38
Number of courses administered					
1	n (%)	327 (100)	4 (100)	N/A	N/A
Completed all 12 infusions		292 (89.3)	3 (75)		
2	n (%)	217 (66.4)	N/A		
Completed all 12 infusions		190 (58.1)			
Exposure (person-years)		261.7	3.3	106.2	16.1

The follow-up time in person-year is calculated as the sum of the duration of study follow-up across all the subjects in the Safety Population. For PROTECT and TN-10 Extension, exposure began the day of the first study drug. For Protégé Extension, exposure was calculated based on date of informed consent as no intervention was administered.

For the ongoing, blinded PROTECT trial, 327 subjects received at least one dose of study drug (teplizumab or placebo) with 261.65 person-years of follow up data for the combined teplizumab and placebo treatment arms. Additionally, 217 subjects received two treatment courses of either teplizumab or placebo (separated by 6 or 12 months).

For the ongoing, open-label TN-10 Extension study, 4 subjects received 1 course each of teplizumab with 3.26 person-years of follow-up data.

In the Protégé Extension study, 181 (82.6%) subjects had received teplizumab and 38 (17.4%) had received placebo during the Protégé study. For the Protégé Extension, teplizumab-treated patients had 106.2 person-years of follow-up data whereas placebo-treated patients had only 16.1 years of follow up data from the date of signed informed consent. Therefore, this reviewer primarily inspected the data for potential drug related AESIs rather than performing incidence rate comparisons.

5.1.1. PROTECT

The PROTECT study is an ongoing, randomized, double-blind, placebo-controlled, multicenter, and multinational trial evaluating the safety and efficacy of teplizumab given to subjects aged 8-17 years old newly diagnosed with T1D (within 6 weeks of diagnosis) as a 12-day course of daily IV teplizumab administered twice, with the second course 6 months or 12 months after the first course.

A total of 327 subjects have been enrolled in the PROTECT study and randomly assigned at a ratio of 2:1 to receive teplizumab or placebo. All subjects are scheduled to be followed through Week 78. While the original protocol stipulated a 2-course dosing regimen administered at randomization and Week 26, the protocol was amended to allow subjects to receive the second course at Week 52 to accommodate infusions that could not be administered due to the COVID pandemic. Per Sponsor communications, only 30 subjects (10% of those enrolled) have been administered the “modified dosing regimen” for teplizumab.

Additionally, in March 2021, subjects randomized to teplizumab started to receive teplizumab manufactured by AGC Biologics (the intended commercial product) while subjects prior to March 2021 received teplizumab manufactured by Lilly (a product from previous clinical trials including TN-10). The sponsor submitted a blinded safety analyses comparing safety data between subjects enrolled prior to March 2021 (N=223) either randomized to Lilly teplizumab or placebo, and subjects enrolled after March 2021 (N=104) either randomized to AGC Biologics

teplizumab or placebo. Review of this analysis can be found in immunogenicity section 5.2.6.

As of this safety update, the treatment arms for the PROTECT study remain blinded. The PROTECT study's last subject was randomized on November 4, 2021, and the last subject, last visit is projected to occur on May 4, 2023.

Per FDA's request, updates from the Data Monitoring Committee (DMC) review of PROTECT (open meeting minutes and the most recent recommendation letter) were submitted on 6/14/2022 (SDN 63) and show there were no new safety concerns with respect to the observed frequency, grade or relationships of adverse events, treatment interruptions or study discontinuations in the PROTECT study.

Since the PROTECT study is currently blinded, for analysis of events that are of low frequency in the general population (i.e., cytokine release syndrome, serious infection and cytopenias), "worst case" safety analyses were completed assuming that all of the detected adverse events occurred in the study occurred in patients randomized to teplizumab. As the blinded study contains 327 subjects, randomized to either teplizumab or placebo in a 2:1 ratio, I adjusted rates of important adverse events to occur out of an estimated 218 subjects randomized to teplizumab, compared with the blinded safety population of 327 subjects treated with either teplizumab or placebo.

5.1.2. TN-10 Extension

TN-10 was a randomized, placebo-controlled, double-blind, parallel-arm efficacy and safety study designed to evaluate the treatment effect of teplizumab compared with placebo in the delay of T1D in individuals with stage 2 T1D, at high risk for developing stage 3 T1D.

The TN-10 Extension study is an ongoing, open-label, multicenter (5 sites in the US) extension trial in subjects who completed the TN-10 trial who were subsequently diagnosed with stage 3 T1D. In the TN-10 extension trial, patients were to initiate open-label treatment with teplizumab within 1 year of diagnosis of stage 3 T1D.

The open-label teplizumab treatment course administered in the TN-10 extension study was the same cumulative dose (9.0 mg/m^2) as the originally studied regimen for TN-10, but administered over a shorter time period, of 12 days. After completing the treatment course, subjects are followed for 78 weeks (18 months) from the first dose of open-label treatment. In addition, subjects had to fulfill all inclusion and exclusion criteria for the TN-10 extension study and sign an informed consent form.

For the original submission, the Applicant included all available safety data for TN-10 up to a median follow up time of 50.6 months of the trial, at the time of trial end, when 43 patients were diagnosed with stage 3 T1D. In this Safety Update, the Applicant provides new safety data for the 4 subjects in the TN-10 Extension study following open-label dosing of teplizumab. Of note, the 4 subjects from the TN-10 Extension study were all randomized to the teplizumab treatment arm in the original TN-10 study, so the open-label teplizumab infusion at the start of the TN-10 Extension study is each subject's second course of teplizumab (per sponsor communication, dated 6/30/2022, SDN 68). As noted in Table 3, 3.3 person-years of follow up were included in the safety update for the N=4 patients enrolled in the ongoing TN-10 extension study.

5.1.3. Protégé Extension

The Protégé Extension study was a 3-year follow-up of the double-blind, placebo controlled Protégé study (CP-MGA031-01). Subjects were invited to participate in the Protégé Extension study if they completed the Protégé study through Day 728 and met all entry criteria. No study treatment was administered in this long-term safety follow-up study.

The original Protégé study was conducted in two parts, segment 1, and segment 2.

- Segment 1
  Segment 1 was an open-label safety study in which 38 subjects with recently diagnosed T1D were given intravenous (IV) teplizumab for 14 days, as two identical courses 6 months apart
- Segment 2
  Segment 2 was a randomized, double-blind, placebo-controlled, double-blind, dose-ranging efficacy and safety study designed to evaluate the treatment effect of teplizumab compared with placebo on the c-peptide area under the curve (AUC) in individuals who had recently been diagnosed with T1D. Protégé segment 2 was designed to assess three teplizumab dosing regimens (a full 14-day course, a one-third dose 14-day course, and a 6-day course) of daily IV infusions compared with placebo (IV) given as two identical courses, 6 months apart.

  Both segments 1 and 2 enrolled patients with recently diagnosed stage 3 T1D, within 12 weeks of diagnosis.

The Protégé Extension study was terminated early by MacroGenics when the Protégé study failed to meet its primary endpoint. This is reflected in the average follow-up time in person-

years for teplizumab-treated subjects (of 6 months) and placebo-treated subjects (of 4.5 months) beyond study day 728.

Thirty-two (14.6%) subjects who completed Protégé Study Segment 1 (open-label) and 187 (85.4%) subjects who completed Protégé Study Segment 2 (double-blind) were included in the safety update population.

As for the role of the Protégé Extension trial in the safety update analysis, it is important to note the limitations of the data for this long-term follow up study. As shown in Table 3, for teplizumab-treated subjects (N=181), there were 106.2 person-years of follow-up, with a median follow-up time of 178 (2-661) days (approximately 0.6 years per person), and for placebo-treated subjects (N=38) there were 16.1 person-years of follow-up, with a median follow up time of 127.5 (22-411) days (approximately 0.4 years per person). This difference in follow-up time in person-years of exposure is due to a combination of a much higher, by approximately 4.7-fold, number of teplizumab-treated subjects (N=181) enrolled in the extension study compared to the number of placebo subjects (N=38) coupled with a 1.4-fold longer median follow-up time, by 50.5 days in the teplizumab group. Therefore, the teplizumab-treated group could be expected to have approximately 5 times the rate of adverse events as the placebo arm when corrected for by study follow-up exposure and enrollment differences.

Overall, limited conclusions can be drawn from the data from the completed Protégé Extension study as there was such a stark a difference in subject follow up between the study arms.

5.1.4. Categorization of Adverse Events

As in the original BLA, the Applicant used the standard medical dictionary for regulatory activities (MedDRA). Adverse events in the PROTECT were coded using version 24.0 of MedDRA, TN-10 Extension using version 24.0 of MedDRA and Protégé Extension using version 23.0 of MedDRA. For the resubmission, the grading scale used to assess severity of events was the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for PROTECT and TN-10 Extension, and version 3.0 for Protégé Extension. In the original submission, grading for studies were unified based on CTCAE version 3.0, the version used for TN-10 and Protégé as well as the Protégé Extension study in the safety update.

For the safety update, the same definition of adverse events of special interest (AESI) were used as were used in the original BLA. Table 4 lists the AESI definitions for the safety update. Grading criteria for AESIs for the studies included in the safety update were specified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for the PROTECT and TN-10 Extension studies and version 3.0 for the Protégé Extension. AESI analyses were

addressed in section 5.2.4 Treatment Emergent Adverse Events, and section 5.2.5 Laboratory Findings.

Table 4. Adverse Events of Special Interest (AESI) for the Safety Update

AESI	Search Criteria	Grading Defined As:
Infections	SOC – 'Infections and infestations'; ≥Grade 3	≥Grade 3 (CTCAE versions 5.0 and 3.0) defined as infection where invasive intervention or IV antibiotic, antifungal, or antiviral intervention is indicated
Acute mononucleosis-like illness	'Mononucleosis syndrome', 'Epstein-Barr virus antibody positive', 'Epstein-Barr virus test positive', 'Epstein-Barr viremia', 'Cytomegalovirus antibody positive', 'Cytomegalovirus test positive', 'Infectious mononucleosis', 'Lymphadenopathy', 'EBV IgM antibody positive'	
Lymphomas or other malignancies	SOC – 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)' and HLT – includes 'malignant' or 'lymphomas)	
Major Hypoglycemia	PT – 'Hypoglycemia', 'Hypoglycemic seizure', 'Hypoglycemic coma'; 'Hypoglycemic unconsciousness'	
Liver function abnormalities	(HLT – 'Liver function analyses'; ≥Grade 3	≥Grade 3 (CTCAE versions 5.0 and 3.0) defined as ALT or AST >5x ULN or total bilirubin >3x ULN
Thrombocytopenia	PT – 'Thrombocytopenia'; ≥Grade 3,	≥Grade 3 (CTCAE versions 5.0 and 3.0) defined as <50,000 platelets/mm^3
Allergic/Hypersensitivity reaction	PT – 'Dermatitis allergic', 'Drug hypersensitivity', 'Anaphylactic reaction', 'Immune reaction', 'Anaphylaxis', 'Hypersensitivity', 'Infusion related reaction', 'Serum sickness'; ≥Grade 4	≥Grade 4 (CTCAE version 5.0), defined as life-threatening consequences, with urgent intervention indicated ≥Grade 4 (CTCAE version 3.0), defined as anaphylaxis
Rash	SOC – 'Skin and subcutaneous tissue disorders'; ≥Grade 3	≥Grade 3 (CTCAE version 5.0) defined as lesions covering >30% body surface area with moderate or severe symptoms ≥Grade 3 (CTCAE version 3.0) Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA
Cytokine Release Syndrome	PT – 'Cytokine release syndrome'	≥Grade 4 (CTCAE version 5.0) defined as Life-threatening consequences or urgent intervention indicated) ≥Grade 4 (CTCAE version 3.0) defined as Life-threatening; pressor or ventilatory support indicated

Lymphocyte count <500 mm^3 for 7 days or longer	PT– 'Lymphopenia'; ≥Grade 3	≥Grade 3 (CTCAE versions 5.0 and 3.0) defined as <500 mm^3 for duration of at least 7 days

Note: Grading criteria for the studies included in the update were specified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for the PROTECT and TN-10 Extension studies and version 3.0 for the Protégé Extension.

5.2. Safety Results

5.2.1. Deaths

There was one death reported in a study included in the safety update, Protégé Extension. However, this death was submitted and reviewed as a part of the original BLA and therefore there is no new information to discuss regarding this case. Refer to the original BLA review, dated July 2, 2021, for further discussion on deaths in the teplizumab development program.

5.2.2. Serious Adverse Events

All serious adverse events (SAEs) in the safety update were reviewed individually with review of patient narratives and in some cases, individual case report forms, patient profiles and laboratories.

In the original BLA, the most commonly reported SAEs for the TN-10 study were in the Infections and Infestations SOC (0% in placebo and 9.1% in teplizumab). However, all infection SAEs in TN-10 occurred greater than 2 weeks after completion of the teplizumab treatment course and were not considered temporally related to observed lymphopenia or temporary immunosuppression associated with teplizumab. In addition, there was one episode of serum sickness in a teplizumab-treated patient approximately 5 days after completion of the 14-day teplizumab course. The other SAEs were isolated events of dizziness, concussion, ankle fracture, musculoskeletal chest pain and pelvic-ureteric obstruction and considered unlikely related to teplizumab treatment due to the lack of temporal relationship to teplizumab dosing and isolated nature of events. For the 5-study pool safety database submitted with the original BLA, the most commonly reported SAEs were diabetic ketoacidosis (0.8% controls vs. 2.5% teplizumab) followed by Infections (2.0% controls vs. 3.4% teplizumab), hypoglycemia (1.2% controls vs.1.7% teplizumab) and cytokine release syndrome (0% controls vs. 0.6% teplizumab).

For the safety update population, 27/550 (4.9%) of all subjects reported SAEs. Of these 27 subjects, about half, 51.8% (14/27) were from the ongoing blinded PROTECT study, and thus, the treatment arm for about half of the reported SAEs for the safety update remain blinded.

PROTECT

Table 5 presents a summary of all SAEs in the PROTECT study by preferred term.

Table 5. Serious Adverse Events (Teplizumab and Placebo) in the PROTECT study

	PROTECT (N=327)		Study Day
Preferred Term	Count [n]	%	
Cytokine release syndrome	3 [3]	0.9%	2-3
Hypoglycemia	3 [2]	0.6%	149, 172, 219
Infection*	2 [2]	0.6%	
Device-related bacteremia			3
Palpitations (related to viral myocarditis)			77
Anxiety	1 [1]	0.3%	22
Colitis ulcerative	1 [1]	0.3%	323
Concussion	1 [1]	0.3%	498
Dermatitis atopic	1 [1]	0.3%	82
Nephrolithiasis	1 [1]	0.3%	220
Suicidal ideation	1 [1]	0.3%	328
Syncope	1 [1]	0.3%	63
Vomiting	1 [1]	0.3%	3

Reporting period: Trial start to November 21, 2021, data is sorted by the number of events
*Starred category contains terms grouped by reviewer, recategorized on review of narratives
Source: Reviewer created from text from resubmission 13-month safety update

Of the 16 SAEs reported by 14 subjects from the ongoing PROTECT study, 3 SAEs were reported to be cytokine release syndrome (CRS), an expected adverse event with teplizumab, in a similar rate (0.9%) to that observed in teplizumab-treated patients in the original BLA safety population (0.6%). For a detailed review of the CRS SAEs, see section 5.2.8, Cytokine Release Syndrome.

Two of the SAEs (device-related bacteremia, and palpitations (related to viral myocarditis) were determined by this reviewer to be related to infections and while the study is still blinded, a causal relationship with treatment is possible due to the timing of each event and associated symptoms. See section 5.2.12.1 for a detailed review of these infection events.

Action taken with respect to study drug for these SAEs included permanent withdrawal of study drug in 3 subjects with CRS SAEs, study drug interrupted in 1 subject, and no action taken in 10 subjects.

Reviewer Comment: The SAEs noted from the blinded analysis of the PROTECT study were either expected with teplizumab use (CRS or infection) or observed in similar, or lower rate than previously demonstrated in the prior teplizumab safety studies. This analysis did not modify the safety profile for teplizumab.

TN-10 Extension

There were no SAEs reported in the TN-10 extension study.

Protégé Extension

For the Protégé extension study, thirteen (13/181, 7.2%) subjects treated with teplizumab in the original Protégé study reported a total of 20 SAEs, shown in Table 5.

Table 5. Serious Adverse Events in the Protégé Extension Study

	Protégé Extension Teplizumab (N=181)		Protégé Extension Placebo (N=38)		Study Day (for isolated events)
Preferred Term	Count [n]	%	Count	%	
Diabetic ketoacidosis	6 [4]	2.2%	0	0	811-1008
Angina pectoris	1 [1]	0.3%	0	0	761
Appendicitis perforated	1 [1]	0.3%	0	0	915
Coronary artery disease	1 [1]	0.3%	0	0	761
Death	1 [1]	0.3%	0	0	980
Diabetes mellitus inadequate control	1 [1]	0.3%	0	0	987
Appendicitis perforated	1 [1]	0.3%	0	0	915
Gastritis	1 [1]	0.3%	0	0	801
Gastroenteritis	1 [1]	0.3%	0	0	729
Hypoglycemic seizure	1 [1]	0.3%	0	0	868
Iritis	1 [1]	0.3%	0	0	793
Peritonitis	1 [1]	0.3%	0	0	915
Spinal compression fracture	1 [1]	0.3%	0	0	868
Spontaneous abortion	1 [1]	0.3%	0	0	814
Varicella	1 [1]	0.3%	0	0	746

Reporting period: Trial start to November 21, 2021, data is sorted by the number of events
Source: Reviewer created from text from resubmission 13-month safety update

All SAEs for the long-term noninterventional Protégé Extension follow-up study were reported, at the earliest, approximately 2 years after enrollment. Additionally, limited conclusions can be drawn from the unblinded SAEs from the completed Protégé Extension as there was a stark difference in subject follow up between the study arms as outlined in section 5, Table 3. Based

on differential follow-up and enrollment, the teplizumab-treated group for the Protégé Extension could be expected to have approximately 5 times the rate of adverse events as the placebo arm when corrected for by study follow-up exposure. It is important to note that DKA events occurred only in patients with stage 3 T1D. In the original BLA, there were no at-risk (stage 2 T1D) patients with adverse event of DKA.

In conclusion, no unexpected pattern or clustering of preferred terms (PTs) was observed, and no new safety concerns were identified based on the reported SAEs from the 2 ongoing clinical trials and the 1 completed trial in the safety update.

5.2.3. Dropouts and/or Discontinuations Due to Adverse Effects

This section first discusses AEs that led to discontinuation of teplizumab treatment for the original BLA safety population followed by each study included in the safety update, focusing on any relevant findings from the safety update that impact labeling.

According to the teplizumab study protocols, teplizumab dosing was to be fully withdrawn if certain clinical laboratory criteria were met (Table 6). This table was included in the original BLA review and updated to include the PROTECT study laboratory and adverse-event related discontinuation criteria for this resubmission review. The two other studies included in the safety update, TN-10 extension and Protégé extension, had the same discontinuation criteria as their primary studies, TN-10 and Protégé, respectively.

Table 6. Prespecified Discontinuation Criteria for Studies in Original Submission + Safety Update

Parameter	TN-10	AbATE	Protégé	Encore	PROTECT
Bilirubin	>1.3 mg/dL on Day 1; ≥2.0 mg/dL on other days	>1.3 mg/dL on Day 1; ≥2.0 mg/dL on other days	>2 times ULN	>2 times ULN	>3 times ULN
AST/ ALT/ LDH	AST level >2 times ULN on Day 1 AST, ALT or LDH ≥3.0 times ULN on other days.	AST level >2 times ULN on Day 1 AST, ALT or LDH ≥3.0 times ULN on other days.	AST or ALT >3 times ULN	AST or ALT >3 times ULN	AST or ALT >5 times ULN ***Or*** AST and/or ALT >3 times ULN AND total bilirubin >2 times ULN (Hy's Law)
Platelet count	<140,000 on Day 1; <100,000 on other days	<140,000 on Day 1; <100,000 on other days	<140,000 on Day 1; <100,000 on other days	<140,000 on Day 1; <100,000 on other days	<50,000
Neutrophils	<1000 cells/mm^3	<1,000 cells/mm^3	<1,000 cells/mm^3 on 2 consecutive evaluations performed on different days	<1,000 cells/mm^3 on 2 consecutive evaluations performed on different days	<500 cells/mm^3

Hemoglobin	≤8.5 g/dL or a drop in ≥2 g/dL compared with prior to infusion to a value <10.0 g/dL	≤8.5 g/dL or a drop ≥2 g/dL to <10 g/dL	<8.5 g/dL or a reduction of >2 g/dL from pre-treatment level	<8.5 g/dL or a reduction of >2 g/dL from pre-treatment level	<8.5 g/dL
Coagulation	INR >0.1 above ULN	INR >1.3	N/A	N/A	NA

Source: Reviewer. The protocol for Delay was not available.
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; INR, international normalized ratio; ISS, integrated summary of safety; LDH, lactate dehydrogenase; ULN, upper limit of normal

Original Safety Population

In the original BLA, 12.5% of teplizumab-treated patients in the safety database did not complete the first cycle of treatment, with the majority of discontinuations related to the laboratory withholding criteria, as detailed in Error! Reference source not found. above. The most common adverse events leading to treatment discontinuation in the original safety population were related to transaminase elevations, for which 5.6% of teplizumab-treated patients and 0.9% of controls discontinued the first course of treatment, followed by decreased hemoglobin (1.8% teplizumab-treated and 0 controls), leukopenia, lymphopenia, and anemia (1.5% of teplizumab-treated and 0.5% controls) and cytokine release syndrome (1% of teplizumab-treated and 0.5% controls).

PROTECT

My analysis of treatment discontinuations for the safety update was primarily limited to the ongoing, blinded PROTECT study.

In general, the laboratory-related discontinuation criteria for PROTECT had higher thresholds (i.e., AST or ALT >5x ULN) compared to the original safety studies in the BLA (i.e., AST or ALT >3x ULN) and as expected, there were fewer study discontinuations observed in this study.

In the PROTECT study, there were 18/327 (5.5%) study discontinuations and 13/327 (4.0%) course 1 treatment discontinuations (i.e., patients who didn't complete the first course of either teplizumab or placebo). 77% of the premature course 1 treatment discontinuations occurred on days 2-3 of treatment. Since PROTECT is still blinded, if all discontinuations were attributed to teplizumab-treated patients (approximately 218 of the 327 randomized), then 5.9% (13/218) of teplizumab-treated patients likely were unable to complete the full course of teplizumab, approximately half the rate of discontinuations observed in the original BLA population (12.5%).

On review of the patient narratives for the 13 patients who didn't complete treatment course

1, three subjects discontinued treatment due to adverse events of cytokine release syndrome (CRS), one due to cellulitis and device-related bacteremia, one due to pregnancy, one where an adverse event was not specified, one due to diarrhea in the context of fever, four discontinued related to elevated liver transaminases meeting discontinuation criteria (with concomitant CRS in 3/4), 1 discontinued due to elevated alanine aminotransferase (ALT), but did not meet protocol-directed laboratory discontinuation criteria as ALT was 2x ULN on study day 6, and 1 discontinued due to elevated bilirubin which was also present 7 days prior to dosing and elevated at baseline. For the discontinuations related to cytokine release syndrome, all were noted on study days 2-3, required hospitalization and were considered resolved within 1-9 days. These are all reasonably likely to be associated with teplizumab except for pregnancy.

In contrast to the original BLA population, where 5.6% of teplizumab-treated patients discontinued treatment due to liver function test abnormalities, for the PROTECT study, only 1.2% (4/327), and in "worst case scenario", 1.8% (4/218) discontinued treatment prematurely due to liver transaminase abnormalities meeting protocol-specified laboratory thresholds for discontinuation. There were no noted premature treatment discontinuations related to thrombocytopenia, lymphopenia, neutropenia, or anemia. The rate of discontinuations related solely to CRS was approximately 0.9% (3/327) or 1.3% (3/218) using "worst case scenario" analysis and is very similar to the rate of discontinuations related to CRS in the original safety database (1%). Given the reduction in discontinuations related to both transaminase elevations and cytopenias, it is likely that more relaxed discontinuation criteria for laboratory-related adverse events of the PROTECT study led to the overall lower rate of discontinuations (up to 5.9%) compared to the original BLA safety population (12.5%).

There is no evidence that the less conservative discontinuation criteria led to prolonged or unresolved laboratory abnormalities.

> *Reviewer comment: The use of less conservative laboratory criteria for discontinuation (specifically for liver enzyme elevations, lymphopenia, neutropenia, thrombocytopenia, and decreased hemoglobin) resulted in fewer treatment discontinuations in the PROTECT study without noted adverse sequelae (see analysis in section 5.2.5, Laboratory Findings). Therefore, the PROTECT study demonstrated that higher laboratory thresholds for discontinuation could be enacted safely in patients receiving teplizumab. For labeling, I recommend providers be informed of the permanent discontinuation criteria used in the PROTECT study, with details regarding the timing and extent of expected laboratory abnormalities, and the timeline for laboratory normalization, without specific recommendations for treatment discontinuation.*

TN-10 Extension

The TN-10 extension had a patient who prematurely discontinued treatment, with 1 of 4 patients completing 11 of 12 infusions due to adverse events of fever and pharyngitis. For the TN-10 extension the sponsor reported no study discontinuations as that patient continued on study following treatment.

Protégé Extension

The Protégé extension study was terminated early by the sponsor, and therefore, all of the subjects included in the safety update discontinued this study prematurely. Given Protégé Extension was a non-interventional follow up study, an analysis of discontinuation events was not performed for this resubmission review.

5.2.4. Treatment Emergent Adverse Events and Adverse Reactions

PROTECT

Similar to the original BLA, lymphocyte abnormalities were commonly reported in the PROTECT study, but were coded under two different system organ classes (SOCs) with preferred terms (PTs) of lymphocyte count decreased (22.3%) and lymphopenia (12.8%).

> *Reviewer comment: In the original BLA, leukopenia and lymphopenia were the most frequently reported AEs. Therefore, despite being blinded, the PROTECT study also reflects a similar adverse event profile for teplizumab treatment.*

The most commonly reported TEAEs in the PROTECT study included hypoglycemia (59.3%), headache (30.6%), nausea (29.7%), rash (24.8%), and vomiting (21.7%). While nausea, rash and vomiting were all expected TEAEs frequently observed in the original BLA safety population, hypoglycemia was not observed as a frequent adverse event, and was reported in 6.8% of subjects in the original BLA safety population (combined treatment arms).

Due to this discrepancy in reported events of hypoglycemia, the sponsor was asked to provide a detailed analysis of hypoglycemia events for the PROTECT study, which were reported in 38.9% of subjects (127/327) within the first 30 days of treatment (either teplizumab or placebo) and 59.3% (194/327) during the entire follow-up period. The sponsor reported that the high rate of hypoglycemia noted in the PROTECT study was largely due to different hypoglycemia reporting criteria from the original BLA studies and the addition of blood glucose recording and reporting by continuous glucose monitoring (CGM) and the inclusion of non-symptomatic hypoglycemia events in adverse event reporting for the PROTECT study.

As the PROTECT study is ongoing and treatment arms are blinded, it is unknown whether the high number of hypoglycemia adverse events are related to teplizumab treatment, or simply a higher reporting rate in a population with stage 3 T1D when CGM monitoring is used. When the analyses of the safety update population from the PROTECT study were limited to clinically significant hypoglycemia events, specifically those requiring treatment with glucagon or associated with seizure, coma or unconsciousness, the risk appeared to be lower in the safety update population than the original BLA population, as shown in Table 7 below.

Table 7. Hypoglycemic Adverse Events Requiring Treatment or Associated with Clinical Events in PROTECT study compared to original BLA safety database

Adverse Event	**Original BLA N=1018** n (%) (Tep/Placebo combined)	**PROTECT N=327** n (%) (Tep/Placebo combined)
Hypoglycemia requiring treatment (glucagon)	7 (0.7%)	3 (0.9%)
Hypoglycemic seizure	6 (0.6%)	0
Hypoglycemic coma	2 (0.2%)	0
Hypoglycemic unconsciousness	4 (0.4%)	0

In order to further characterize and compare hypoglycemia between the PROTECT study and the original BLA safety population, the Sponsor performed an analysis to equilibrate the hypoglycemia analyses from the original BLA dataset with the safety update population (which used CGM and had a different definition of hypoglycemia) via assessing local and central laboratory reports for blood glucose levels in the original safety database. Based on this analysis, detailed in Table 8 below, a similar proportion of subjects experienced laboratory hypoglycemia at each level. Further, it should be noted that more severe low blood glucose levels <54 mg/dL were reported in a lower proportion of subjects in the Safety Update Population.

Table 8. Summary of Sponsor's evaluation of laboratory reports (local and central laboratories) for blood glucose levels in the original safety population compared to the PROTECT study

	Original Safety Population		
Glucose Level	Teplizumab N=791 n (%)	Placebo N=245 n (%)	PROTECT N=327 (Tep/Placebo)
55-69 mg/dL	261 (33)	67 (27.3)	62 (19)

40-54 mg/dL	115 (14.5)	27 (11.0)	56 (17.1)
30-39 mg/dL	20 (2.5)	8 (3.3)	1 (0.3)
<30 mg/dL	8 (1.0)	2 (0.8)	3 (0.9)
54 mg/dL and below	132 (16.7)	34 (13.9)	13 (4)
30 mg/dL and below	27 (3.4)	10 (4.1)	4 (1.2)

Reviewer comment: Overall, when we look at TEAE other than hypoglycemia, the analysis for TEAEs in PROTECT are consistent with the original safety review. Upon further investigation of the hypoglycemia signal, I agree with the Sponsor's conclusion that this signal is largely driven by the reporting of non-symptomatic hypoglycemia events by continuous glucose monitoring, as focused analysis clearly demonstrated no increase in rates of symptomatic hypoglycemia events from the original safety population.

Diabetes-specific AEs related to insulin use like hypoglycemia are not unexpected in a trial population of patients with recent-onset stage 3 T1D. Similar to the original review, we do not expect common AEs observed in the T1D patient population in the safety update like hypoglycemia to be applicable to the intended population.

TN-10 Extension

In the TN-10 Extension study, two subjects reported treatment-emergent adverse events of nausea and headache. Otherwise, the following TEAEs were reported by one subject each: cellulitis, COVID-19, pharyngitis, pruritus, rash, bradycardia, pyrexia, cytokine release syndrome (CRS), eosinophil count increased, lymphocyte count decreased, white blood cell count decreased, pharyngeal erythema, and hypertension. On review of the severity grading, the majority of these TEAEs, 69%, were mild in severity. The adverse events with severity greater than mild were headaches (moderate) and expected laboratory-related adverse events of lymphocyte count decreased in levels expected based on teplizumab's known pharmacodynamic profile.

Reviewer comment: The individual TEAEs reported in the 4 patients from the TN-10 Extension study who received open-label teplizumab are consistent with AEs observed in the prior teplizumab safety program, including cytokine release syndrome, laboratory abnormalities, and infection.

Protégé Extension

Comparative TEAE analyses were not performed for the Protégé Extension given the study is a long-term non-interventional follow-up study with lack of adequate comparator follow up time.

5.2.5. Laboratory Findings

Laboratory data included in this resubmission

As part of this safety update, the Applicant included blinded by-subject data for Epstein-Barr virus (EBV) and cytomegalovirus (CMV) viral loads by quantitative polymerase chain reaction (PCR) and EBV and CMV serologies (IgG and IgM) for all PROTECT subjects with available data. In the PROTECT study, EBV and CMV quantitative PCR (copies/mL) were collected at baseline, day 28, 84, 210, 273, 364 and 546 and serologies were collected at baseline.

Other than viral titers and serologies for the blinded PROTECT study, no other raw laboratory data or laboratory data analyses were submitted as a part of this resubmission. As the PROTECT study remains blinded, the viral titers and serologies were not analyzed as a part of this safety update review.

Laboratory-related adverse event analysis

Laboratory-related adverse events were common in the original BLA review, especially cytopenias (lymphopenia, leukopenia, neutropenia, thrombocytopenia), decreased hemoglobin, and liver function test abnormalities. In the resubmission safety update, the sponsor included an analysis of specific laboratory-related adverse events that were defined as adverse events of special interest (AESI) in the PROTECT study. As presented in Table 6, and discussed in Section 5.2.3, the PROTECT study had less conservative laboratory-related adverse event withdrawal criteria, resulting in fewer discontinuations (approximately 5.5% versus the original BLA safety pool of 12.5%) and fewer discontinuations attributed to laboratory-related adverse events (approximately 2.7% versus the original BLA safety pool of 9.9%). Therefore, analyses were performed by the FDA to assess rates of lymphopenia, neutropenia and liver function test abnormalities reaching a specific threshold in the PROTECT study in order to evaluate if the more relaxed discontinuation criteria resulted in any additional safety concerns not observed in the original safety population. It was thought that the rates of certain laboratory abnormalities (lymphopenia, neutropenia, thrombocytopenia, anemia, and liver function abnormalities) meeting the AESI thresholds are low enough in the general population to assume that all AESI were due to teplizumab and therefore, “worst case scenario” analyses were used to further evaluate the safety profile of teplizumab for the currently blinded

PROTECT study.

Lymphopenia meeting AESI threshold, a lymphocyte count <500 cells/m^3 for 7 days or longer, was reported in 3/327 (0.9%) of subjects in the PROTECT study, and in "worst case scenario" 1.3% (3/218) of teplizumab-treated subjects. On review of the individual patient profiles, one patient was noted to have lymphopenia (200 to <500 cells/m^3) on study day 4, with resolution by study day 55. Study treatment was paused for 1 day with resumption and completion of the entire course of study treatment. The other two cases of lymphopenia were noted starting within 2-3 days of study drug infusion initiation and resolved within 1 week of noting the AE without modification of study drug treatment.

Neutropenia meeting threshold, <1000 polymorphonuclear leukocytes/uL on two consecutive evaluations, was reported in 5/327 (1.5%) of subjects in the PROTECT study, and in "worst case scenario" 2.2% (5/218) of teplizumab treated subjects. In all cases, this AESI was noted within 2-4 days of initiating the study drug, with resolution within 1-6 days despite continued treatment in 3 subjects, or temporary (1 day) dose withholding in 2 subjects.

In terms of liver function test abnormalities, there were 6/327 (1.8%) of subjects who met criteria, and in "worst case scenario" 2.7% (6/218) of teplizumab treated subjects. Four subjects had alanine aminotransferase (ALT) increased (>5x ULN to 20x ULN), three with aspartate aminotransferase (AST) increased (>5x ULN to 20x ULN) and one with blood bilirubin increased (>3x to 10x ULN). Of the subjects with increased ALT, the events were reported study days 4-9 and study drug was discontinued in all cases, with normalization of ALT within 5-22 days of drug discontinuation. Of the subjects with increased AST, this AE was first noted on study days 2-9 with resolution following 1 day of dose interruption in one subject and resolution within 8-20 days of study drug discontinuation in two subjects. For the subject with blood bilirubin increased, this was noted day 4 of study drug and resolved within 8 days of study drug discontinuation. In summary, all subjects noted to have abnormal liver function tests meeting threshold were discontinued from drug with documented recovery of the adverse event within 22 days of discontinuation.

> *Reviewer comment: I conducted a review of individual patient reports for laboratory-related adverse events reported as adverse events of special interest (AESI) for the PROTECT study. While the study remains blinded, the reports of recovery despite continued treatment for cases of lymphopenia and neutropenia were overall reassuring and lead to the conclusion that drug pausing criteria could be safely included in the labeling (as opposed to drug discontinuation criteria) for lymphopenia and neutropenia. For cases of liver function test abnormalities, the current discontinuation criteria proposed in the labeling (ALT*

or AST (b) (4) ULN and total bilirubin (b) (4) ULN) appear to be appropriately protective, with the resolution of all cases of ALT/AST/bilirubin elevations following discontinuation at this threshold.

5.2.6. Immunogenicity

Please refer to the original BLA review (section 8.4.10).

The resubmission and safety update included new unblinded immunogenicity (ADA) data from the PROTECT study.

The PROTECT study collected information on Anti-drug antibodies (ADA) at baseline (pre-treatment), day 12, 28 and 56 and subjects were considered to have overall positive ADA status if there was at least one confirmed post-baseline positive result on day 12, 28 or 56. Overall, ADA were identified in 93.3% (126/135) of teplizumab-exposed subjects with available data in the PROTECT study compared to the original BLA safety population, where ADA were observed in 50 to 92% of teplizumab-exposed patients in Protégé, Encore and TN-10, during the first course of teplizumab across the various treatment regimens, and the incidence of ADA was as high as 90% when a second course was administered.

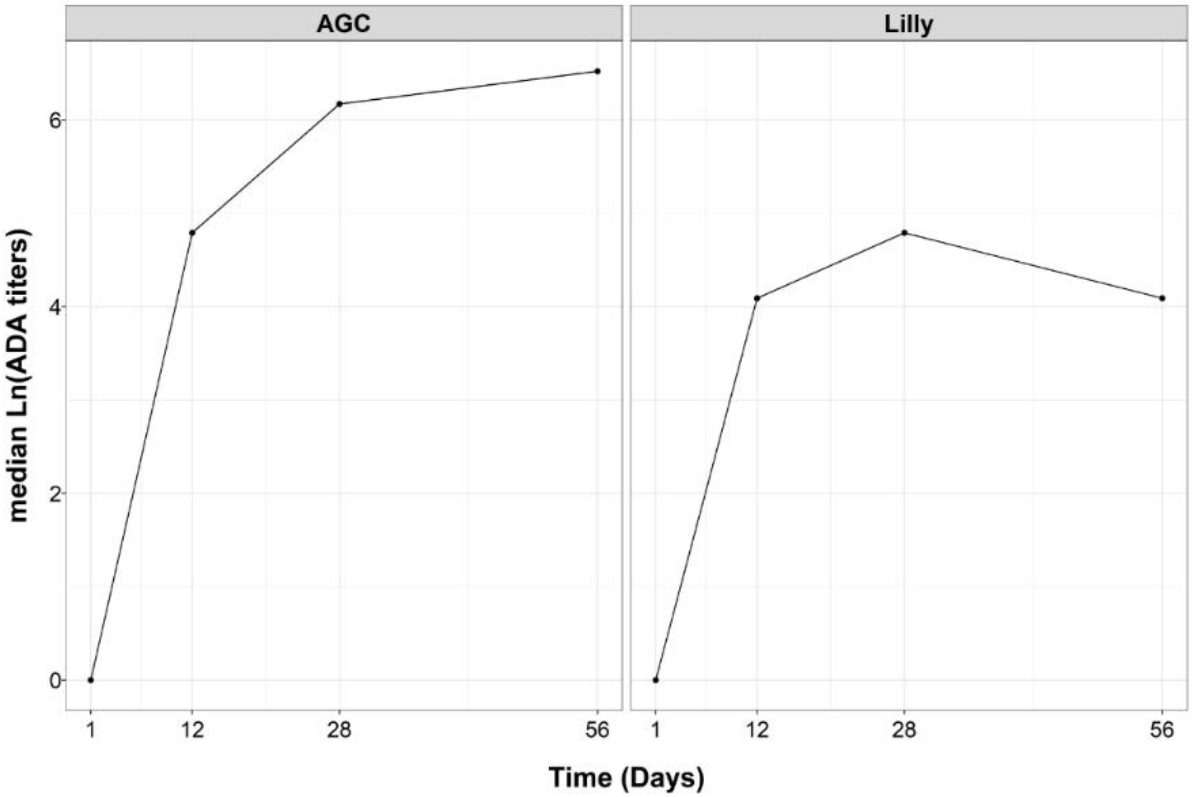
Unblinded immunogenicity results for 32 subjects treated with AGC biologics and 137 subjects treated with Lilly were available for review. There were comparable rates of immunogenicity observed in the subjects randomized to the AGC biologics product (31/33, 93.9%) compared to the subjects randomized to the Lilly product (95/102, 93.1%) at 52 weeks. However, patients treated with the AGC biologics product compared to the Lilly product, tended to have earlier ADA appearance, as illustrated in an analysis provided by the FDA Pharmacometrics reviewer, Table 9 below, with higher ADA titers, as illustrated in Figure 1 below.

Table 9. Proportion of subjects with appearance of ADA (grouped by titer) at each study day grouped by product (AGC vs. Lilly) for the PROTECT substudy

	AGC product (N=32)	Lilly product (N=137)	PROTECT sub-study (N=169)
maximum Ln(ADA Titer) levels			
Missing	0 (0%)	28 (20.4%)	28 (16.6%)
Null	2 (6.3%)	37 (27.0%)	39 (23.1%)
0 < value < Ln(30)	2 (6.3%)	0 (0%)	2 (1.2%)
value ≥ Ln(30)	28 (87.5%)	72 (52.6%)	100 (59.2%)
Ln(ADA Titer) levels on Day 12			
Missing	1 (3.1%)	36 (26.3%)	37 (21.9%)
Null	6 (18.8%)	38 (27.7%)	44 (26.0%)
0 < value < Ln(30)	3 (9.4%)	8 (5.8%)	11 (6.5%)
value ≥ Ln(30)	22 (68.8%)	55 (40.1%)	77 (45.6%)
Ln(ADA Titer) levels on Day 28			
Missing	5 (15.6%)	38 (27.7%)	43 (25.4%)
Null	4 (12.5%)	38 (27.7%)	42 (24.9%)
0 < value < Ln(30)	1 (3.1%)	0 (0%)	1 (0.6%)
value ≥ Ln(30)	22 (68.8%)	61 (44.5%)	83 (49.1%)
Ln(ADA Titer) levels on Day 56			
Missing	4 (12.5%)	41 (29.9%)	45 (26.6%)
Null	3 (9.4%)	43 (31.4%)	46 (27.2%)
0 < value < Ln(30)	1 (3.1%)	4 (2.9%)	5 (3.0%)
value ≥ Ln(30)	24 (75.0%)	49 (35.8%)	73 (43.2%)

Source: Generated by FDA Pharmacometrics Reviewer from nonmemdata4studs14jun22.xpt (SD 65, 6/17/2022)

Figure 1. Median titer level (in log titer) for subjects randomized to AGC vs. Lilly by study day



Source: Generated by FDA Pharmacometrics Reviewer from nonmemdata4studs14jun22.xpt (SD 65, 6/17/2022)

Because PROTECT is ongoing, at this time it is not possible to examine the relationship between ADA and efficacy and safety outcomes.

5.2.7. Blinded AEs for AGC vs. Lilly

This reviewer evaluated blinded AE reports by product (AGC vs. Lilly). In total, the adverse event analysis includes data from 223 patients who either received Lilly teplizumab or placebo and 104 patients who either received AGC teplizumab or placebo. No meaningful differences were apparent.

5.2.8. Cytokine Release Syndrome

CRS is considered an important safety signal in the teplizumab development program. Among the original BLA safety population, CRS events were identified in up to 5% of teplizumab-treated patients using the Applicant's analysis based on Common Terminology Criteria for

Adverse Events (CTCAE) version 3.0 criteria, and there were 7 patients (0.9% of the teplizumab treatment group) who required hospitalization for CRS.

For the safety update population, 3/327 (0.9%) subjects in the PROTECT study had SAEs of CRS which all occurred within the first three days of study drug administration requiring hospitalization. If it is assumed that all cases occurred in teplizumab-exposed patients, the incidence rate is 1.5%. Importantly, the reviewed CRS cases resemble the previously reported CRS cases in the original BLA with respect to severity, onset, and symptoms. In all three cases, the study treatment was discontinued, and each subject was discharged from the hospital within 48 hours of admission. One of the subjects, a 9 year-old male, required intravenous fluid and a single dose of epinephrine for hypotension.

The sponsor evaluated the data for possible differences in adverse event frequency between the AGC and Lilly products. 16/223 (7.2%) of the subjects treated with either Lilly or placebo reported AE of CRS, compared to 1/104 (1%) of the AGC or placebo-treated subjects.

None of subjects (N=4) in the TN-10 Extension study experienced SAEs of CRS, with one reported TEAE of CRS. The non-interventional Protégé Extension was not considered relevant for the analysis of CRS.

Reviewer comment: The safety update information does not change the original safety conclusions with respect to CRS.

5.2.9. Hypersensitivity/ Rash

In the safety update, AEs with the PT of 'hypersensitivity' were reported in 1/327 (0.3%) of PROTECT subjects and no patients in the TN-10 Extension study. The sponsor performed an additional analysis at the request of the Agency (received 6/14/2022, SDN 63) which revealed 2/327 (0.6%) of PROTECT subjects reporting the PT of 'infusion related reaction'. These 3 AEs were mild to moderate in severity, considered by the investigators to be related to study drug and recovered despite continued treatment with study drug. There were no reported adverse events with the following PTs: 'anaphylaxis', 'drug hypersensitivity', 'immune reaction' or 'serum sickness' reported in either the PROTECT or TN-10 Extension studies. The noninterventional Protégé Extension study was not considered relevant for this analysis due to the inclusion of only safety data at least 2 years after teplizumab dosing.

There were no SAEs of rash in the safety update. Rash was noted as one of the common AEs for the PROTECT study 81/327 (24.8%), consistent with previous observations in the clinical program. One rash was reported in the TN-10 extension study, 1/4 (25%). The

noninterventional Protégé Extension study was not considered relevant for this analysis due to the inclusion of only safety data at least 2 years after teplizumab dosing.

Reviewer comment: The safety update information does not change the original safety conclusions with respect to hypersensitivity/rash.

5.2.10. Lymphopenia

Lymphocyte abnormalities and white blood cell (WBC) abnormalities occurred in up to 22% of teplizumab-treated subjects in the PROTECT study, consistent with the original BLA safety data where a consistent association between lymphopenia was observed though placebo-controlled phase 3 data.

5.2.11. Evaluation of Potential Drug Induced Liver Injury

No laboratory analyses were included for the studies included in the safety update; however, no cases of potential drug induced liver injury were reported.

5.2.12. Infections

5.2.12.1 General Infections

In the safety update population, there were 2 infection SAEs, both in the PROTECT study. The first SAE was reported to be "IV-related bacteremia" and "cellulitis" starting after the 3rd infusion of study drug treatment. During the hospitalization, this subject was found to have staphylococcal bacteremia and started on oral antibiotics with resolution of symptoms and the AE following treatment. A temporal relationship with lymphopenia was observed in this this subject, and although the lymphopenia in this case was mild, it is plausible that temporary immunosuppression from teplizumab may have contributed to the development of cellulitis and bacteremia despite the baseline risk of this AE from an indwelling catheter. It should be noted that this subject has not yet been unblinded so the treatment is currently unknown, and no safety conclusions can be made based on this case.

Another subject (blinded to treatment assignment) had experienced a viral infection requiring hospitalization during the PROTECT study. This subject, a 15 year-old female, initially presented with a SAE of palpitation to the emergency room and was found to have abnormally elevated troponin 125 ng/L (normal range <16.47 ng/L) and was diagnosed with myocarditis and mild pericardial effusion on thoracic echocardiography, requiring hospitalization. This SAE occurred from study days 76-82, approximately 2 months after completion of the first course of either teplizumab or placebo. Following outpatient cardiology consultation after hospital discharge it

was determined that the myocarditis and pericarditis were due to Coxsackie B4 virus infection based upon the viral serology of 1:640. This subject also had experienced recent infectious mononucleosis reactivation from study day 29-43 with complete resolution of EBV viral titers by study day 137 when EBV viral titers were <200 copies/mL. It is possible that temporary immunosuppression contributed to this patient's development of viral myocarditis, although the case report did not contain enough information to conclude that the subject was experiencing immunosuppression (lymphopenia or neutropenia) at the time of this infection event. On evaluation of these two events in a currently blinded study there are barriers and limitations in the assessment of causality. However, even in the setting of a blinded study, the possibility for infection with teplizumab use remains biologically plausible and continues to be recommended as a Warning & Precaution in labeling.

> *Reviewer comment: As noted in the original BLA review, infection secondary to immunosuppression is an important safety issues of interest for teplizumab. While the safety update does not contribute additional information beyond two cases of infection in PROTECT study patients currently blinded to treatment arm, the individual case narratives continue to reflect that infection remains a potential issue with teplizumab use. Therefore, it remains prudent to continue to recommend a Warning and Precaution for a potential risk of serious infection as a risk mitigation measure.*

5.2.12.2 Epstein-Barr Virus (EBV) Infection

In the safety update, the Sponsor repeated an analysis for "acute mononucleosis-like illness" using the PROTECT study and the most common events reported by this analysis were "lymphadenopathy" reported in 8/327 (2.4%) of the subjects, who remain blinded to treatment assignment. According to the sponsor's analysis, none of the cases were associated with clinical symptoms or a diagnosis of mononucleosis or mononucleosis-like syndrome, or positive EBV or cytomegalovirus (CMV) viral titer elevation on review of the case reports. There was 1 subject (0.3%) each reporting Epstein-barr viraemia and Epstein-barr virus infection and 5 subjects with "EBV test positive" listed as an adverse event in PROTECT (1.5%, 5/327). There was little additional information from the safety update regarding this signal, but the sponsor submitted detailed reports representing the current (blinded) safety data they have collected on each subject (including EBV and CMV quantitative PCR (copies/mL) collected at baseline, day 28, 84, 210, 273, 364 and 546 and serologies at baseline). Therefore, the safety update included reassuring safety data that the sponsor will continue to collect adequate safety data related to EBV/CMV infections for the PROTECT study to further understand this risk upon future analysis of the unblinded data.

5.2.13. Diabetic Ketoacidosis

For the safety update, there were no DKA events reported in the PROTECT study (which remains blinded) or the TN-10 extension study.

For the Protégé Extension study, 1.7% (3/181) teplizumab-treated subjects experienced DKA SAEs. By comparison, DKA SAEs occurred in 1.9%, of the teplizumab-treated original BLA safety population. All DKA events were reported as SAEs, and no patients treated with placebo reported DKA events. One subject reporting two events of DKA in the Protégé Extension population also experienced two DKA events during the original Protégé study (reported as a part of the original BLA safety analyses). There are some limitations to interpreting adverse events reported during the Protégé Extension study as there was a difference in safety exposure information between the study arms in the Protégé Extension study, which may lead to a 5-fold higher rate of adverse events among the teplizumab arm, which had higher enrollment and follow-up time than the placebo arm. Overall, similar rates of DKA were observed among the Protégé Extension study as the original BLA safety population with stage 3 T1D.

> *Reviewer comment: While a higher proportion of teplizumab-treated patients (1.7%) versus control patients (0%) experienced DKA events in the long-term follow up period of the Protégé Extension study, the rate of DKA is similar to the rates observed in the teplizumab-treated patients in the original BLA safety analyses. Additionally, there are limitations to interpreting this data given the follow up period was greater for teplizumab-treated patients.*

5.3. Safety Analyses by Demographic Subgroups

In the original application, our analyses demonstrated that there were no important safety differences significant treatment-emergent adverse events (cytokine release syndrome, infections, cytopenias, hepatic enzyme elevations) among subgroups by age, sex, and race. The safety update did not contain enough unblinded demographic and safety information to perform these analyses in the update population which contained data from two blinded, ongoing studies and one unblinded long-term follow-up study.

5.4. Additional Safety Explorations

5.4.1. Human Carcinogenicity or Tumor Development

The number and types of cancers reported from the updated data were reviewed. There were no events from TN-10 Extension or Protégé Extension studies which met criteria for lymphoma

or malignancy.

For the PROTECT study, there were two reported events for the SOC "lymphoma or other malignancies", one for AE term "papilloma" with verbatim term "verrucae planae juveniles" for an 8 year old female starting 52 days after the first dose of study treatment (teplizumab or placebo), and the second "papilloma" AE term with verbatim term "warts right foot" for an 11 year old male which was noted 35 days after the first dose of study treatment (teplizumab or placebo).

As verrucae or warts are common in children, and the treatment group remains blinded, it is possible that these events are unrelated to study treatment dosing in both cases. Similar to the original BLA, we did not detect a safety signal related to cancer for the safety update.

For details regarding the original BLA human carcinogenicity assessment please refer to the original review (July 2, 2021). It is important to note that the clinical safety data submitted in the original BLA was not sufficient to evaluate the potential risk of malignancy or lymphoproliferative disease because of the short duration of follow-up as well as the relatively young age of the safety population. The longest trial duration available in publication is the 7-year follow-up of the AbATE trial (n=43), and this trial reported no malignancy among the 43 patients treated with two courses of teplizumab (given 1 year apart). Following this safety update, there were no notable signals for malignancy, but uncertainty remains regarding rare or long-latency risks which could be addressed through the creation of a postmarketing patient registry for approximately 10 years in order to assess further the risk of malignancy.

5.4.2. Human Reproduction and Pregnancy

Since the original submission, one pregnancy was reported during PROTECT. This participant discontinued course 1 treatment and the treatment group remains blinded at the time of this safety update. Per the Data Monitoring Committee (DMC) open minutes, the pregnancy resulted in a healthy baby.

5.5. Safety in the Postmarket Setting

5.5.1. Expectations on Safety in the Postmarket Setting

The teplizumab clinical trials in the original BLA submission had broadly similar discontinuation criteria that provided a standardized approach to discontinuing drug treatment, with provisions to stop treatment for laboratory abnormalities including bilirubin and aminotransferase

elevations, or abnormal platelet, neutrophil, hemoglobin, or coagulation parameters, and the occurrence of certain adverse events. If this approach to treatment discontinuation is applied in the postmarket setting, it is estimated that approximately 10% of patients will not be able to complete the full course of teplizumab therapy. This rate of treatment discontinuation is expected in the post-market setting if similar drug discontinuation criteria are put in place in labeling.

Less stringent laboratory and adverse event-based discontinuation criteria were used for the PROTECT study, with an observed lower rate of discontinuations related to adverse events, at 3.7%. While the PROTECT study remains blinded, if these discontinuations are attributed to patients only treated with teplizumab in worst-case scenario analyses, the discontinuation rate would be 5.5%, approximately half the discontinuations observed in the original safety database.

On review of the individual narratives for each laboratory adverse-event related discontinuation, including discontinuations related to aminotransferase elevations, neutropenia and lymphopenia, each adverse event resolved following either the discontinuation of product, withholding dosing for 1-2 days, and in the majority of cases of neutropenia and lymphopenia, despite continued treatment with study drug. Notably, there were no serious adverse events related to continued treatment among patients who would have met premature treatment discontinuation criteria. This reviewer therefore concludes that more serious or permanent harms are not expected if less restrictive discontinuation criteria (from the PROTECT study) are reflected in teplizumab's approved labeling. Additionally, the PROTECT study provided reassuring support that laboratory related adverse events were reversible, even after application of less stringent discontinuation criteria, and therefore the PROTECT study discontinuation criteria adequately mitigate risk of severe adverse events and can be safely adopted in the postmarketing period. A discussion on the discontinuation criteria and findings from this analysis are discussed extensively in section 5.2.5, Laboratory Findings.

Otherwise, there are no other modifications to the expectations of safety in the postmarket setting based on the safety data included in this resubmission. Please refer to the original review, dated 7/2/2022 for details regarding safety expectations and section 6 for proposed labeling and section 8 for Postmarketing Requirements and Commitments.

5.6. Integrated Assessment of Safety

The integrated assessment of safety is not meaningfully changed with the safety update.

6. Labeling Recommendations

6.1. Prescription Drug Labeling

Labeling recommendations are contained within this review as appropriate.

The labeling issues discussed during this submission included the following:

1. Update to proposed language for the Established Pharmacologic Class
2. Update to proposed language for the indication statement
3. Updated with revised dosing regimen based on recommendations of the clinical pharmacology review team
4. Inclusion of laboratory safety data for the PROTECT study in section 6.1, Clinical Trial Experience, Laboratory Abnormalities
5. Additional information regarding serious infection signal observed in the clinical trial populations in warnings and precautions
6. Inclusion of additional information related to immunogenicity in Section 12.6, and
7. Revision of information in Clinical Trials limiting Table 1 to adverse event data from the only study in the indicated population (TN-10) with descriptive trial data for studies conducted in the unapproved population (stage 3 type 1 diabetes) where appropriate.

7. Risk Evaluation and Mitigation Strategies (REMS)

No REMS was recommended for the original BLA and this recommendation continues upon this resubmission based on no new significant safety signals noted in this resubmission.

During the original BLA primary review, the Division of Risk Management (DRM) and DDLO discussed potential FDA-driven communications close to the time of approval to highlight the novel treatment for patients with stage 2 T1D and to convey safety information regarding cytokine release syndrome (CRS). Given the extension to the PDUFA timeline for this application, this FDA-driven communication will be composed after the completion of this primary review.

8. Postmarketing Requirements and Commitments

The Pediatric Research Equity Act (PREA) requirement is discussed in the original BLA review, dated July 2, 2021. This section discusses potential (Food and Drug Administration Amendments Act of 2007) FDAAA-related postmarketing requirements (PMRs) and postmarketing commitments (PMCs). The final decision about PMRs/PMCs is deferred to the CDTL memo.

During the original review we identified the following safety issues, for which we considered a PMR safety study: CRS, infection, and longer latency events like LPD or other malignancy. The Applicant was notified of these potential PMR issues during the mid-cycle communication meeting for the original submission.

At the time of the initial review, we determined that malignancy is a safety issue that cannot reasonably be resolved in a premarket development program for teplizumab, and therefore considered a 10-year registry study with long-term follow-up for documentation and evaluation of any events of malignancy as a conservative approach to address any uncertainty about the potential safety issue.

Regarding the safety risks of cytokine release syndrome (CRS), and lymphoproliferative disease, we are not currently recommending any postmarketing requirements (PMRs) or postmarketing commitments (PMCs) for further characterization of these events; these events should be reported in routine Periodic Safety Update Reports.

Following advice from DPMH, we initially recommended a pregnancy study for women and their offspring who are exposed to teplizumab during pregnancy in order to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. However, it is anticipated that pregnancy with use of teplizumab (a 14-day course) would be exceedingly rare as the treatment is transient. Given the recommended screening for pregnancy prior to treatment and that the population of intended use consisting primarily of youth and adolescents being treated for a very limited time period (14 days) we anticipate that there will be minimal numbers of pregnancies and that any study performed in this way would be of limited value.

9. Appendix

9.1. Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators (submitted on 6/14/2022, SDN 63). Due to the PROTECT PK/PD substudy being an important source of PK data for the Population PK modeling, this study was included in the evaluation of financial disclosures for the resubmission.

Covered Clinical Study (Name and/or Number): PROTECT PK/PD Substudy (PRV-031-001)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 46		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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07/14/2022 03:24:30 PM

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